Environmental Organochlorine Exposure as a Potential Etiologic Factor in Breast Cancer

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Known risk factors for breast cancer do not account for a significant proportion of the overall incidence. Reproductive factors and endogenous hormones are thought to be responsible for a large component of risk. An environmental contribution has been sought in the past to explain the international trends in breast cancer rates and changes in risk among migrating populations. Recently, environmental research has turned to investigation of exogenous chemical exposures, including environmental contamination, as potential risk factors that may arise from the hormonal activity or from the carcinogenicity of many of these chemicals. Several reports since 1991 suggest that organochlorines may be a risk factor for breast cancer. The data are strongest for DDT. For PCBs, the results to date have been equivocal if not entirely negative. However, different groups of polychlorinated biphenyl (PCB) congeners are known to provoke biological responses that are structure specific. A wide divergence of estrogenic response, cytochrome P450 activity, and biological half-life exists within these groups of PCB congeners. Therefore, understanding breast cancer risk from PCB exposure requires attention to congener structures in complex mixtures and to temporal changes in exposure. Investigation of environmental contributions to breast cancer risk offers the potential for understanding more about the etiology of this complex disease and may also provide opportunities for prevention of the most common cancer among women in the United States. — Environ Health Perspect 103(Suppl 7):141–145 (1995)

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Introduction

Reproductive history and hormonal factors are widely accepted as major risk factors for breast cancer. Environmental exposures may also be important in breast cancer etiology, as indicated by international variations in incidence and studies of migrant populations. However, research on specific environmental chemicals that may contribute to breast cancer risk is in its infancy. Recently, preliminary data have emerged suggesting that breast cancer risk may be associated with exposure to persistent organochlorines. This class of chemicals includes DDT, chlordane, polychlorinated biphenyls, hexachlorocyclohexane, kepone, and polybrominated biphenyls. These chemicals are carcinogenic in animals and are sequestered in fatty tissues. Their lipid solubility, low volatility, and chemical inertness lead to their residence in the body for a lifetime.

Interest in the relationship of these chemicals to breast cancer arose because, in addition to their persistence and carcinogenicity, certain of these chemicals are able to mimic the activity of reproductive hormones in laboratory tests and in wildlife. In addition, one research group made two observations among women that suggested a hormonal effect of DDT; Rogan and colleagues at the National Institute of Environmental Health Sciences (NIEHS) (*1*) reported that women with higher levels of DDE reported shorter durations of lactation. DDE is the major residue of DDT in the environment, and it is usually found in humans at higher levels and more frequently than any other organochlorine.

Epidemiologic Investigation of Organochlorines and Breast Cancer Risk

Four recent case–control studies have linked environmental organochlorine exposures to breast cancer risk (Table 1). A fifth study reported no statistically significant differences in DDE between cases and controls, although the results for the African–American and Caucasian subgroups were consistent with previous studies. The relative risks reported in these studies are in the range of 2 to 10, so that they rank among the higher risks observed for breast cancer in the epidemiologic literature. The evidence is strongest in supporting a relationship between DDT and breast cancer. An earlier study while not disproving this hypothesis failed to find an association (*2*). Apart from DDT, the data for other organochlorines have not shown any consistent associations, but polychlorinated biphenyls (PCBs) and hexachlorocyclohexane ([HCH] or benzene hexachloride [BHC]) were significantly elevated in two studies.

The first was the study by Frank Falck et al. (*3*), showing approximately 50% higher levels of DDE, DDT, and higher chlorinated PCBs among 20 breast cancer cases, compared with 20 controls. No significant differences were found for hexachlorobenzene (HCB) or chlordane residues. HCH was not detected. The risk for DDT although elevated, was not statistically significant. There was approximately 1% increased risk for every 10 ppb of DDE and PCBs in adipose tissue. While a striking association was observed in this study, its import is limited by the pilot nature of the design, which did not allow adjustment for potential confounding reproductive factors.

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Abbreviations used: DDT, bis(4-chlorophenyl)-1,1,1-trichloroethane; DDE, bis(4-chlorophenyl)-1,1-dichloroethene; PCBs, polychlorinated biphenyls; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; NIEHS, National Institute of Environmental Health Sciences; HCH, hexachlorocyclohexane; BHC, benzene hexachloride; HCB, hexachlorobenzene; ppb, parts per billion; PAH, polycyclic aromatic hydrocarbons.

Table 1. Case–control studies of breast cancer and DDT exposure.

	Cases	Controls	
Davies, 1974 (*26*)	29	29	—
Wassermann et al., 1976 (*27*)	9	5	Tumor > normal mammary tissue
Albert et al., 1982 (*28*)	8	7	Tumor > normal mammary tissue
Unger et al., 1984 (*2*)	14	21	—
	18	35	—
Mussalo-Rauhamaa et al., 1990 (*5*)	44	33	—*
Falck et al., 1992 (*3*)	20	20	~3 (67th > 33rd percentile)
Wolff et al., 1993 (*4*)	58	171	~4 (10th-90th percentile)
Dewailly et al., 1994 (*6*)	18	17	ER+: 9 (67th > 33rd percentile)
Krieger et al., 1994 (*7*)	150	150	—**

*Relative risk of ~10 seen for women whose BHC (HCH, hexachlorocyclohexane) levels were above 0.1 ppm in adipose. **Adjusted trends showed risks of 2 to 4 (not statistically significant) in the upper terciles of black and white women (50 cases and controls in each group).

The second study was part of the the New York University Medical Center Women's Health Study cohort (*4*). Blood serum specimens from 58 breast cancer cases, collected 1 to 6 months before diagnosis, and 171 individually matched controls from the same cohort were available. As with the Falck study, levels of DDE were significantly higher among breast cancer cases than among controls. PCB levels were also higher among cases, but the differences were not statistically significant. Women in the upper decile of serum DDE had about 4-fold increased risk compared with those having the lowest concentrations. There was approximately 9% increased risk for every 1 ppb of DDE in blood serum. Since the usual concentration of chemicals in adipose tissue is approximately 200 times that in blood serum, these data were comparable to the findings in the Falck study (*3*).

Similar risks for breast cancer were found among Finnish women with elevated levels of β-hexachlorocyclohexane, a lindane-derived residue (*5*). A recent report from Canada found significantly higher levels of DDE in estrogen receptor-positive breast cancer cases compared with controls (*6*).

A fifth study used blood serum that had been gathered during the late 1960s in a California health maintenance organization 1 to 20 years before cancer diagnosis (*7*). Levels of serum organochlorines were compared among 150 breast cancer cases (one-third each Caucasian, African–American, and Asian) and an equal number of controls from the same cohort. Although there were no differences in DDE and PCB levels when the three groups were considered in the aggregate, serum DDE levels appeared to be as important a risk factor among African–American and Caucasian women (but not among Asians) as in previous studies (Table 2).

In summary, the current status of the case–control studies relating breast cancer risk to organochlorine exposure suggests a relationship with DDT exposure (Tables 1, 2). The magnitude of the estimated risks from the recently cited studies is similar to the risks that have been estimated using data from experimental animals (*8,9*).

PCBs and Breast Cancer Risk

The evidence for risk from exposure to PCBs and other organochlorines is equivocal, but there are interesting trends in the available data for PCBs that merit further study. Since PCBs occur as complex mixtures, their biological effects might be expected to represent an integrated response to the individual components of these mixtures. However, all but one of the cited reports have used total PCBs as the exposure measure. Total PCBs as found in humans can represent the sum of 10 to 40 PCB congeners, depending on the laboratory method and on an individual's exposure.

An alternative approach is to investigate the PCB exposures in a congener-specific fashion, which may reveal structure–activity relationships like those observed in experimental animals. A first important example is the potential for a range of estrogenic and antiestrogenic activity for congeners with specific chlorine substitution patterns (Figure 1)(*10*). Second, persistence, or resistance to metabolism, is also stereospecific. A third inherent PCB property, the potential for inducing cytochrome P450 enzymes, also varies according to structure (Table 3). Three possible structure–activity groups (I, II, III) can be established that categorize these properties.

Their currently recognized estrogenic response may be characterized as estrogenic, antiestrogenic, and neither (groups I–III; Figure 1, Table 3). It is apparent that the estrogenic PCB congeners (group I) are characterized by a chlorine pattern that is also known to be more rapidly metabolized than the coplanar or typical persistent congeners (Table 3)(*11*). Group I congeners have two adjacent nonsubstituted lateral carbon atoms on at least one of the biphenyl

Table 2. Relative risks for terciles of DDE exposure in studies of breast cancer.

DDE levels, ng/ml	≤1	≤5	≤10	≤15	≤20	≤25	≤30	≤35	≥40	
Krieger et al., 1994 (*7*)										
Whites, DDE tercile mean				14				31	72 ppb	
OR (*n*) $p=0.24$				1.0				1.8	2.4	
Blacks, DDE tercile mean						23			44	102 ppb
OR ($n=100$) $p=0.07$						1.0			2.0	3.8
Asians, DDE tercile mean					20				43	89 ppb
OR ($n=100$) $p=0.52$					1.0				0.9	0.7
Falck et al., 1992 (*3*)										
Whites, estimated DDE tercile		2.3	7.6	13 ppb						
OR ($n=40$)		1.0	3.6	13.3						
Wolff et al., 1993 (*4*)										
Whites, estimated DDE tercile	1.0		8.5		16 ppb					
OR ($n=229$)	1.0		1.9		3.5					
Dewailly et al., 1994 (*6*)										
Whites, estimated DDE tercile	1.2	3.8	6.5 ppb							
OR ($n=35$)	1.0	3.0	8.9							

Abbreviation: OR, odds ratio. Regression coefficient, b, was used to estimate OR for Wolff, b=0.0823; Falck, b=0.00122; and Dewailly, b=0.00207 (ER+ only, $n=9$), applied to DDE levels among 17 controls. These coefficients were statistically significant. Wolff, Falck, and Dewailly data for terciles were computed from mean ±1 SD, and ORs were computed from the stipulated logistic regression coefficients. The Falck and Dewailly data were given for adipose concentrations that have been converted to approximate serum concentrations by dividing by 200. The Falck adipose terciles were 466, 1526, 2585 ng/g for pooled means ±1 SD of cases and controls. The Dewailly terciles were 238, 765, and 1292 ng/g for controls.

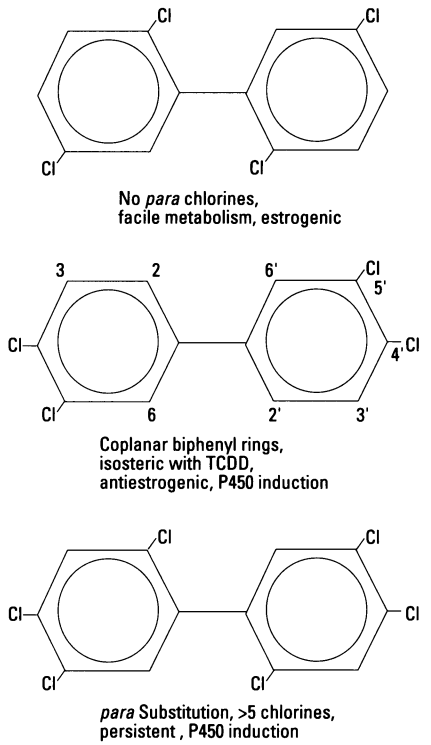

Figure 1. Structure–activity relationships for PCB congeners (*para*-, 4-; *meta*-, 3- or 5-; *ortho*-, 2- or 6-).

rings by definition, including one or two unsubstituted 4 or *para* positions. PCBs with this structure, including the Aroclor 1221 mixture that contains numerous congeners from this group, have estrogenic activity, as documented by their ability to increase uterine weight and cause precocious puberty (*12*), to bind to the estrogen receptor (*13*), and to enhance proliferation of MCF-7 breast tumor cells (*14*).

Group II PCBs have 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD)- or dioxinlike properties that have been shown to be antiestrogenic. Their antiestrogenicity is thought to arise from interaction with the Ah receptor. This receptor best fits congeners that can achieve coplanar stereochemistry of the biphenyl rings (*10*). The structural requirement for coplanarity is the absence of 2, 6, or *ortho* chlorines. The most active congeners are substituted at the 3,4 positions on both biphenyl rings. As a result, these non-*ortho* substituted congeners have no chlorines on the 2 (or the equivalent 6) positions, providing an avenue for metabolism at these adjacent unsubstituted carbon atoms, albeit not as facile as for group I. Therefore, the coplanar PCBs may be more persistent than group I and yet more readily metabolized than the very persistent congeners in group III. Also, some PCBs with a single *ortho* chlorine appear to retain some of the characteristics of group II. For example, the mono-*ortho* PCB 2,3′,4,4′,5,5′-hexaCB is approximately a 100-fold less active than the non-*ortho* analog 3,3′,4,4′,5-pentaCB (*10*).

The antiestrogenic effects of the PCB congeners in group II could lead to protection against breast cancer and could counteract the estrogenic activity of other PCB congeners. TCDD administration to rats caused a decrease in normally occurring breast and uterine tumors and in chemically induced mammary tumors (*15,16*). TCDD and structural analogs including the coplanar PCBs are antiestrogenic in the MCF-7 breast cancer line (*10*). Mixtures exhibit properties consistent with their multiple components. Thus, while the estrogenic PCB mixture Aroclor 1221 causes precocious puberty (*12*), another mixture (Clophen A-50, which contains many antiestrogenic congeners) delays onset of puberty in female rats(*17*). Similarly estrogenic organochlorines support implantation and pregnancy, while TCDD inhibits implantation (*18*).

Group III congeners are highly substituted, persistent PCBs. Some of these congeners may have weak estrogenic activity (*19*). Moreover, their extensive chlorination means that both 2 and 4 positions are substituted in many congeners and that there are few if any adjacent unsubstituted carbons. These configurations are not amenable to metabolism, and therefore these PCBs are very persistent in the body.

In addition to the diverse estrogenicity and metabolic rate of these three groups, the ability to induce cytochrome P450 isozymes also varies according to chlorine substitution pattern. Group II congeners induce the CYP1A family through their binding with the Ah receptor, an effect that is similar to induction by 3-methylcholanthrene or TCDD. Group III shows activity more like that of phenobarbital, inducing the CYP2B family of cytochrome P450 enzymes. There is some overlap in the ability of PCB congeners to induce enzyme activity, so that group III may induce the CYP1A1 group to some extent and CYP2A1 may be induced by both groups II and III (*20*).

From Table 3, it can be seen that marked differences in persistence of PCB congener types also limit the period of time following exposure during which a biological effect could take place. Group I's estrogenic activity would be available for only a few months before elimination was complete in humans. The antiestrogenic effects of the coplanar PCBs in group II may prevail longer than group I, but such activity may exist over a shorter time period than the effects of other, noncoplanar congeners in group III. From this line of reasoning, the risk for breast cancer from exposure to group II could be hypothesized to be lower in the short term (e.g., protective effect of antiestrogenic exposures) and higher in the long term (e.g., persistent exposures to a carcinogen and to an inducer of carcinogen-metabolizing enzymes). It has also been postulated that group II compounds are protective by facilitating metabolism of estradiol to a less genotoxic estrone, the 2-hydroxy isomer (*21*). Group III, on the other hand, may affect cancer over the long term by influencing estradiol metabolism to the more toxic 16α-hydroxy isomer and by enhancing metabolism of carcinogens. In addition, some congeners in this category may also act as hormonal agonists (*19*).

In summary, both the hormonal activity and the metabolic profile of persistent organochlorines must be taken into account in assessment of their long-term effects. The evidence to support this concept comes mainly from experimental data such as that cited above. Human data are limited. There is no evidence for an association of PCBs with breast cancer from the few reported mortality studies (*22*). However, the exposure measures in these reports relied only on duration of exposure, not on any personal or biological measures or on any information on PCB congeners. Also these studies were based on mortality, rather than incidence, data. Very limited data from studies of dioxin-exposed groups

Table 3. Potential PCB biological activity according to congener structure.

Isomers	Activation	Persistence, half-life	Effect
Low chlorination	Hydroxylation	— (months)	Estrogenicity
0 to 1 *ortho* chlorine, coplanar	Ah receptor, CYP1A, (CYP2A)	± (1–5 years)	Antiestrogen, EGFR, metabolism of carcinogens and estradiol (to 2-hydroxy)
>1 *ortho* chlorine	CYP2B, (CYP2A, 1A1)	++ (>10 years)	Metabolism of carcinogens and estradiol (to 16α-hydroxy)

Table 4. Breast cancer incidence (CI) and mortality studies in populations exposed to TCDD.

	Breast cancer	Exposure	Relative risk
Bertazzi et al. (*29*)		Seveso	
	1 case	Zone 1—most exposed	0.5
	10 cases	Zone 2—less exposed	0.7
	106 cases	Zone R—little exposure	1.1
Manz et al. (*30*)	9 deaths	Manufacture of TCP, 2,4,5-T	2.15
Flesch-Janys et al. (*31*)	10 deaths	Manufacture of HCH, phenoxys	2.37 CI 1.3–4.0

suggest that short-term exposures to TCDD may show a protective effect (e.g., in Seveso), while long-term exposures to TCDD and other organochlorines in manufacture show slightly elevated risk (Table 4). Further studies, taking into account the complex qualitative nature of toxicity including the stereospecificity and toxicokinetics of organochlorines, should be undertaken to examine the health risks of such exposures.

Conclusions

Several mechanisms, not necessarily mutually exclusive, can be proposed to explain the association between organochlorine exposure and breast cancer risk. First, since they mimic estrogens in experimental studies, organochlorines may serve as cancer promoters in the same fashion as steroid hormones do. That is, estrogen promotes tumorigenesis in animal experiments, and epidemiologic evidence supports a similar mechanism in humans. *In vitro* experiments demonstrate the ability of estrogen and its synthetic analogs to cause proliferation of breast cancer cells in culture (*14,23*). Moreover, estrogenic chemicals modulate the expression of certain oncogenes, and their potential estrogenic character may dispose organochlorines to be cancer promoters through this mechanism.

Second, a cogent model can be developed around the ability of these chemicals to induce cytochrome P450 enzymes. These enzymes bioactivate many chemical carcinogens such as polycyclic aromatic hydrocarbons (PAH), the prototypical animal model for chemical carcinogenesis, including breast cancer. P450 also metabolizes estrogen, which can lead to genotoxic DNA adducts. Finally, a possible nonbiological explanation for these associations may be that persistent organochlorines act as a surrogate measure for carcinogenic dietary factors or other early exposure to carcinogens that have not yet been identified in epidemiologic studies.

DDT and PCB levels in the U. S. population are gradually receding, thanks to the success of regulatory action in the 1970s (*24*). If the studies linking organochlorines to breast cancer hold true, then the number of affected women may be limited to those with exposures during 1950 to 1972. However, DDT is still widely used in developing countries where it may affect public health or cross international borders. Other environmental exposures deserve attention for their potential influence on breast cancer. There are myriad other potentially estrogenic chemicals in commerce that we are not able to detect long after exposure, such as atrazine and methoxychlor (*25*). Another prime candidate for breast cancer initiation is the family of PAHs, which are rapidly metabolized and cannot be traced long after exposure. The reported greater risk of breast cancer among women who began smoking at an early age suggests that we should study environmental exposures to this class of chemicals early in life. Unfortunately it will be difficult to obtain adequate dose-metrics for such chemical exposures into epidemiological studies.

Nevertheless, in spite of the difficulties in exposure assessment and whether breast cancer risk from organochlorines holds up to further scrutiny, we should actively seek out other possible chemical carcinogens in the environment, current or past, that could also be involved in breast cancer risk. In addition, in both animal research and human epidemiological studies, we should seek to identify biological mechanisms to explain how such risk may come about.

Rates of breast cancer occurrence in the United States have steadily risen since 1940. During that same period, levels of pesticide and PCB residues in human adipose tissue in the United States have shown parallel increase, following their introduction into commerce around the time of World War II. Since then, despite much research on the question, only three factors have been generally agreed to be strongly linked to breast cancer: age, country of birth, and family history. These factors are not readily amenable to change. Medicine has done its job well in finding new avenues of treatment and detection, and hence the mortality rates have been stable over the recent past. However, the existence of a cure without a cause continues because no pathways for prevention have been found. We hope that our research may be a step in the direction of prevention as well as to better understanding the cause of breast cancer.

Three recent publications provide further relevant information. In describing a new analytic method, Djordjevic et al. (*32*) observed higher levels of several pesticides including DDT, as well as PCBs, among 5 cases compared with 5 controls (difference not statistically significant). Gladen and Rogan (*33*) confirmed the negative impact of DDE on duration of lactation in a second group of women from Mexico. Finally, p,p′-DDE demonstrated antiandrogenic responses both *in vitro* and *in vivo* in the rat (*34*), observations that underscore the importance of investigating a range of hormone function for environmental contaminants (*35*).

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